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JGP

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General Physiology is the study of biological mechanisms through analytical investigations, which decipher the molecular and cellular mechanisms underlying biological function at all levels of organization.

The mission of the *Journal of General Physiology* is to publish articles that elucidate important biological, chemical, or physical mechanisms of broad physiological significance.

ARTICLES

1 **Functional characterization and molecular cloning of the K^+-dependent Na^+/Ca^{2+} exchanger in intact retinal cone photoreceptors.** Christophe Paillart, Robert J. Winkfein, Paul P.M. Schnetkamp, and Juan I. Korenbrot

17 **Open channel block by Ca^{2+} underlies the voltage dependence of *Drosophila* TRPL channel.** Moshe Parnas, Ben Katz, and Baruch Minke

29 **Depolarization-induced calcium responses in sympathetic neurons: relative contributions from Ca^{2+} entry, extrusion, ER/mitochondrial Ca^{2+} uptake and release, and Ca^{2+} buffering.** Michael Patterson, James Sneyd, and David D. Friel

57 **Pharmacological dissection and distribution of NaN/Nav1.9, T-type Ca^{2+} currents, and mechanically activated cation currents in different populations of DRG neurons.** Bertrand Coste, Marcel Crest, and Patrick Delmas

79 **Muscle chloride channel dysfunction in two mouse models of myotonic dystrophy.** John D. Lueck, Ami Mankodi, Maurice S. Swanson, Charles A. Thornton, and Robert T. Dirksen

Cover picture: Photocurrents measured in a dark-adapted single cone isolated from striped bass retina. Peak photocurrent amplitude increases with light intensity up to a saturating amplitude. Current reflects the electrogenic activity of a K^+-dependent, Na^+/Ca^{2+} exchanger, which causes changes in intracellular free Ca^{2+}, as measured with a fluorescent dye (see article by Paillart et al., 1–16).

JGP

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MEETING SUMMARY

95 The 60th symposium of the society of general physiologists. chemotaxis, invasion, and phagocytosis: from bacteria to humans. (Organized by Sergio Grinstein and Joseph J. Falke). Lawrence G. Palmer

COMMENTARIES

101 Gating rings formed by RCK domains: keys to gate opening. Christopher J. Lingle

ARTICLES

109 Gating and inward rectifying properties of the MthK K^+ channel with and without the gating ring. Yang Li, Ian Berke, Liping Chen, and Youxing Jiang

121 The role of S4 charges in voltage-dependent and voltage-independent KCNQ1 potassium channel complexes. Gianina Panaghie and Geoffrey W. Abbott

135 Importance of hydration and dynamics on the selectivity of the KcsA and NaK channels. Sergei Yu. Noskov and Benoît Roux

145 The location of a closed channel gate in the $GABA_A$ receptor channel. Moez Bali and Myles H. Akabas

161 Gain-of-function mutations in the MEC-4 DEG/ENaC sensory mechanotransduction channel alter gating and drug blockade. Austin L. Brown, Silvia M. Fernandez-Illescas, Zhiwen Liao, and Miriam B. Goodman

175 Voltage sensor movement and cAMP binding allosterically regulate an inherently voltage-independent closed–open transition in HCN channels. Shan Chen, Jing Wang, Lei Zhou, Meena S. George, and Steven A. Siegelbaum

189 Acknowledgment

Cover picture: Minimal model of the gating processes in MthK, which involves three conformational equilibria: pH-dependent assembly/disruption of the gating ring (state I and II); Ca^{2+}/pH-dependent gating ring conformational shifts between open and closed states (state II and III), and Ca^{2+}/pH-independent open/closed transitions of the channel pore (state III and IV) (see article by Li et al., 109–120).

JGP

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ARTICLES

191 **Thermosensitive TRPV channel subunits coassemble into heteromeric channels with intermediate conductance and gating properties.** Wei Cheng, Fan Yang, Christina L. Takanishi, and Jie Zheng

209 **A role for the S0 transmembrane segment in voltage-dependent gating of BK channels.** Olga M. Koval, Yun Fan, and Brad S. Rothberg

221 **Corelease and differential exit via the fusion pore of GABA, serotonin, and ATP from LDCV in rat pancreatic β cells.** Matthias Braun, Anna Wendt, Jovita Karanauskaite, Juris Galvanovskis, Anne Clark, Patrick E. MacDonald, and Patrik Rorsman

233 **Phosphomimetic mutation of Ser-187 of SNAP-25 increases both syntaxin binding and highly Ca^{2+}-sensitive exocytosis.** Yan Yang, Tim J. Craig, Xiaohui Chen, Leonora F. Ciufo, Masami Takahashi, Alan Morgan, and Kevin D. Gillis

245 **Acidic amino acids impart enhanced Ca^{2+} permeability and flux in two members of the ATP-gated P2X receptor family.** Damien S.K. Samways and Terrance M. Egan

257 **Quantal release of ATP in mouse cortex.** Yuriy Pankratov, Ulyana Lalo, Alexei Verkhratsky, and R. Alan North

Cover picture: FRET measurement from a HEK 293 cell coexpressing TRPV3_Cerulean and TRPV3_eYFP. Spectroscopic images (center panels) are taken from a thin section of the cell (indicated by the rectangle in left panels). Emission spectrum (right panels) is constructed selectively from the plasma membrane (see article by Cheng et al., 191–207).

JGP

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ARTICLES

267 **Alteration of epithelial structure and function associated with PtdIns(4,5)P_2 degradation by a bacterial phosphatase.** David Mason, Gustavo V. Mallo, Mauricio R. Terebiznik, Bernard Payrastre, B. Brett Finlay, John H. Brumell, Lucia Rameh, and Sergio Grinstein

285 **G551D and G1349D, two CF-associated mutations in the signature sequences of CFTR, exhibit distinct gating defects.** Silvia G. Bompadre, Yoshiro Sohma, Min Li, and Tzyh-Chang Hwang

299 **Structural determinants of the closed KCa3.1 channel pore in relation to channel gating: results from a substituted cysteine accessibility analysis.** Hélène Klein, Line Garneau, Umberto Banderali, Manuel Simoes, Lucie Parent, and Rémy Sauvé

317 **Uncoupling and turnover in a Cl^-/H^+ exchange transporter.** Michael Walden, Alessio Accardi, Fang Wu, Chen Xu, Carole Williams, and Christopher Miller

331 **Cooperation of the conserved aspartate 439 and bound amino acid substrate is important for high-affinity Na^+ binding to the glutamate transporter EAAC1.** Zhen Tao and Christof Grewer

COMMUNICATION

345 **A conformation change in the extracellular domain that accompanies desensitization of acid-sensing ion channel (ASIC) 3.** Kenneth A. Cushman, Josephine Marsh-Haffner, John P. Adelman, and Edwin W. McCleskey

Cover picture: Depletion of phosphatidylinositol 4,5-bisphosphate alters epithelial morphology and actin distribution. Intestinal epithelial cells (IEC18) were microinjected with cDNAs encoding SigD, a bacterial phosphoinositide phosphatase and PLCδ-PH-GFP (green), a probe for phosphatidylinositol 4,5-bisphosphate. Samples were imaged by confocal microscopy at early (2 h; top) and late (5–6 h; bottom) stages after microinjection and stained for F-actin (red). X-Y scans (left and center) and X-Z reconstructions (right) are shown (see article by Mason et al., 267–283).

JGP

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PERSPECTIVES

351 **Perspectives on membrane protein insertion, protein–bilayer interactions, and amino acid side hydrophobicity.** Olaf Sparre Andersen

353 **Formation of transmembrane helices in vivo—is hydrophobicity all that matters?** Gunnar von Heijne

357 **Experimental measures of amino acid hydrophobicity and the topology of transmembrane and globular proteins.** Richard Wolfenden

363 **Membrane protein insertion: the biology–physics nexus.** Stephen H. White

371 **Partitioning of amino acid side chains into lipid bilayers: results from computer simulations and comparison to experiment.** Justin L. MacCallum, W.F. Drew Bennett, and D. Peter Tieleman

COMMENTARIES

379 **Calcium channels are models of self-control.** Kathleen Dunlap

ARTICLES

385 **Elementary mechanisms producing facilitation of $Ca_v2.1$ (P/Q-type) channels.** Dipayan Chaudhuri, John B. Issa, and David T. Yue

403 **Probing the cavity of the slow inactivated conformation of *shaker* potassium channels.** Gyorgy Panyi and Carol Deutsch

419 **Multiple forms of cardiac myosin-binding protein C exist and can regulate thick filament stability.** Irina Kulikovskaya, George B. McClellan, Rhea Levine, and Saul Winegrad

429 **Age decline in the activity of the Ca^{2+}-sensitive K^+ channel of human red blood cells.** Teresa Tiffert, Nuala Daw, Zipora Etzion, Robert M. Bookchin, and Virgilio L. Lew

437 **A direct demonstration of closed-state inactivation of K^+ channels at low pH.** Thomas W. Claydon, Moni Vaid, Saman Rezazadeh, Daniel C.H. Kwan, Steven J. Kehl, and David Fedida

Cover picture: Different approaches to determine hydrophobicity scales. The top two panels show (left) an experimental approach to determine the efficiency of membrane integration of α-helical segments, and (right) a "biological" hydrophobicity scale depicting the apparent free energy change (ΔG^{aa}_{app}) for placing each of the amino acids in the middle of a 19-residue-long α-helical segment (see article by von Heijne, 353–356; figure originally published in Hessa, T., H. Kim, K. Bihlmaier, C. Lundin, J. Boekel, H. Andersson, I. Nilsson, S.H. White, and G. von Heijne. 2005. *Nature.* 433:377–381). The bottom three panels show snapshots from molecular dynamics simulations to calculate the potential of mean force for moving amino acid side chain analogs from the aqueous phase into the bilayer (red and white sticks are water; DOPC phosphate and nitrogen groups are orange and blue spheres, the remainder is rendered as light gray lines). For the side chains: cyan, carbon; white, hydrogen; blue, nitrogen; and red, oxygen. (Left) Gln at 0.4 nm from the bilayer center is stabilized by a water defect; (center) Gln at 0.3 nm from the bilayer center has no associated water defect; (right) Arg at the bilayer center is stabilized by a water defect (see article by MacCallum et al., 371–377).

JGP

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COMMENTARIES

457 **And yet it moves: conformational states of the Ca^{2+} channel pore.** Riccardo Olcese

ARTICLES

461 **Block of $Ca_V1.2$ channels by Gd^{3+} reveals preopening transitions in the selectivity filter.** Olga Babich, John Reeves, and Roman Shirokov

477 **Ca^{2+}-dependent inactivation of $Ca_V1.2$ channels prevents Gd^{3+} block: does Ca^{2+} block the pore of inactivated channels?** Olga Babich, Victor Matveev, Andrew L. Harris, and Roman Shirokov

485 **Vesicular ATP is the predominant cause of intercellular calcium waves in astrocytes.** David N. Bowser and Baljit S. Khakh

493 **Ca^{2+}–secretion coupling is impaired in diabetic Goto Kakizaki rats.** Tobias Rose, Suad Efendic, and Marjan Rupnik

509 **Subunit-specific contribution of pore-forming domains to NMDA receptor channel structure and gating.** Alexander I. Sobolevsky, Michael L. Prodromou, Maria V. Yelshansky, and Lonnie P. Wollmuth

527 **Aspartate-444 is essential for productive substrate interactions in a neuronal glutamate transporter.** Shlomit Teichman and Baruch I. Kanner

Cover picture: A series of images taken at increasing times (from left to right) before and after mechanical stimulation of a central astrocyte (indicated by the star). The top panels show the raw images, the middle panels the wavefront images, and the bottom panels 3D projections (see article by Bowser and Khakh, 485–491).